IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Fastrez et al.
Serial No.	:	08/978,607
Filed	:	November 26, 1997
For	:	***CHIMERIC TARGET MOLECULES HAVING A REGULATABLE ACTIVITY***
Group Art Unit	:	1642
Examiner	:	T. Saidha

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Name of Applicant, Assignee or Registered Representative

Signature

January 14, 2002
Date of Signature

Assistant Commissioner for Patents
Washington, D.C. 20231

AMENDMENT Under 37 C.F.R. § 1.111

Marked up version

Sir:

In response to the Official Action mailed August 14, 2002 (the "Official Action"), Applicants respectfully request entry of this Amendment. A response was due on November 14, 2002, however, a petition for a two (2) months extension of time from November 14, 2002 to January 14, 2003 is enclosed. Therefore this Amendment is timely filed.

IN THE CLAIMS:

29. (Amended) The method of claim 20 [13], wherein the enzymatic activity of the chimeric enzyme in the unbound state is equivalent to that of the starting enzyme.

30. (New) A method for determining the presence or amount of an analyte in a test sample, comprising:

forming a mixture of (1) a chimeric enzyme comprising an enzyme and a binding site moiety, said binding site moiety including at least one amino acid, said chimeric enzyme having a sequence of said binding site moiety inserted in said enzyme or replacing at least one amino acid of said enzyme with the proviso that the activity of the chimeric enzyme is modulated upon binding of a binding molecule to the binding site moiety, (2) a test sample containing said analyte of interest, (3) a binding molecule which binds to a binding site moiety of the chimeric enzyme and modulates the activity of the enzyme, and (4) a substrate upon which the chimeric enzyme catalytically acts; and

detecting the amount of catalysis of the substrate and thereby determining the presence or absence of said analyte of interest.

31. (New) A method of claim 30, wherein the analyte competes with the chimeric enzyme for binding to the binding molecule.

32. (New) A method of claim 30, wherein the binding molecule is said analyte.

33. (New) A method of claim 30, wherein the binding molecule is an antibody.

34. (New) A method for determining the presence or amount of an analyte in a test sample, comprising:

forming a mixture of (1) a chimeric enzyme comprising an enzyme and a binding site moiety, said binding site moiety including at least one amino acid, wherein said chimeric enzyme

having a sequence of said binding site moiety inserted in said enzyme or replacing at least one amino acid of enzyme with the proviso that the activity of the chimeric enzyme is modulated upon binding of a binding molecule to the binding site moiety, (2) test sample containing said analyte of interest, and (3) a substrate upon which the chimeric enzyme catalytically acts; and

detecting the amount of catalysis of the substrate and thereby determining the presence or absence of said analyte of interest.

35. (New) A method of claim 34, wherein the analyte is an antibody.

36. (New) A method of claim 34, wherein the starting enzyme is β-lactamase.

37. (New) The method of claim 30, wherein the enzymatic activity of the chimeric enzyme in the unbound state is equivalent to that of the starting enzyme.

38. (New) The method of claim 34, wherein the enzymatic activity of the chimeric enzyme in the unbound state is equivalent to that of the starting enzyme.

REMARKS

Favorable reconsideration and allowance are respectfully requested. Claims 13-29 are pending in this application.

By this amendment, claim 29 has been amended and claims 30-38 have been added to further define the invention.. No new matter has been added. Support for new claims 30-38 is found on page 2 of the specificaition. Accordingly, upon entry of this amendment, claims 13-38 are pending in this application.

No additional fee is believed necessary for entry and consideration of the enclosed claims. However, the Commissioner is hereby authorized to charge any defeciency or credit any overpayment to Deposit Account No. **50-0540**.

1. The Examiner rejects claims 13-29 under 35 USC 112, first paragraph, as allegedly not being enabled by the disclosure of the instant specification.

The Examiner alleges that "the disclosure is enabling only for claims limited to a method of determining the amount of an analyte in a test sample using a chimeric β-lactamase as the starting enzyme, and comprising selected amino acids sequence insert in the loop of the rim of the active site residues 103-105, for example; or for the alpha 11 helix residues 271-272 of the R-Tem β-lactamase, for example; in order that the enzyme be defined as a chimeric enzyme, which are then selected for binding by antibodies psa10 and psa66" (Official Action, page 2).

Applicants urge that it is unclear how the Examiner arrives at the conclusion that the claims are enabled only for the specific embodiments described in the working examples of the specification. Applicants submit that there is no reasonable basis to assert that the claims be limited to the specific working examples set forth in the application. The specification provides clear guidance to enable any person skilled in the art to select a starting enzyme and a binding site moiety such as a mimetope, select an insertion site and thereby produce chimeras. The specification also provides a working example of a method for determining the amount of an analyte in a test sample using a chimeric β-lactamase as the starting enzyme.

The Examiner appears to be basing the rejection on an argument that there are no working examples for using starting enzymes other than β-lactamase. Applicants respectfully submit that the "enablement" requirement of the first paragraph of 35 U.S.C. §112 requires nothing more than objective enablement. Whether this is achieved by illustrative examples or by broad terminology is of no importance. *In re Marzocchi*, 169 U.S.P.Q. 367 (CCPA 1971). An assertion by the Patent Office that the enabling disclosure is not commensurate with the scope of the protection sought must be supported by evidence or reasoning substantiating the doubt so

expressed. *In re Dinh-Nguyen*, 181 U.S.P.Q. 46 (CCPA 1974); *In re Bowen*, 181 U.S.P.Q. 48 (CCPA 1974); *In re Armbruster*, 185 U.S.P.Q. 152 (CCPA 1975).

It is improper to reject claims on the ground that the specification does not support the claims when the terms of the claim are no broader than the broadest description of the invention in the specification and there is no reason to challenge the operativeness of the subject matter embraced by the claims. *Ex parte Altermatt*, 183 U.S.P.Q. 436 (POBA 1974). Moreover, there is no requirement that an applicant provide a working example of his invention. See *In re Strahilevitz*, 668 F.2d 1229, 1232, 212 USPQ 561, 563 (CCPA 1982). Therefore, the fact that the working examples are limited to the use of β-lactamase does not provide a sufficient basis to reject the present claims.

The Examiner further alleges "[the mimetope] insertion into any enzyme [...] will not necessarily result in producing an active chimeric enzyme in every other enzyme because every other enzyme is distinct in its sequence, regions of active site or susceptibility to modifications, leading to highly unpredictable results" (Official Action, page 4).

Applicants respectfully traverse. Contrary to the Examiner's suggestion, the specification need not provide examples or specific description of every embodiment for the entire scope of the invention. More importantly, the specification clearly teaches a skilled artisan to select a starting enzyme and a binding site moiety insertion site (e.g., a mimetope insertion site) at a location preferably remote from the active site of the enzyme. The use of a site selection remote from the active site preserves the activity of the starting enzyme in the chimeric construct. Applicants submit that information relating to the activity of enzymes of interest is known to any person of skill in the art and available through multiple public and commercial databases. In addition, the specification provides 78 examples of mimetope sequences. The specification also

provides sufficient disclosure and guidance to enable a person of ordinary skill in the art to obtain such a chimeric enzyme without undue experimentation (Specification, pages 2-9).

Furthermore, Applicants urge the Examiner that specific sequence or structure information is unnecessary for modifying a starting enzyme for the desired activity. A chimera that retains the activity of the starting enzyme can be identified with routine screening and without undue experimentation. The level of skill in the art is high and given the extensive guidance that is provided in the specification together with the knowledge of those skilled in the art of genetic engineering and molecular biology, a chimeric molecule, using any starting molecule, can be prepared without undue experimentation. All that is required of the skilled artisan to practice the invention is to identify a starting material, prepare a library of mimetopes and insert the sequences into the starting material and screen for the activity.

Alternatively Applicants have specifically described employing the three-dimensional structure in one of the techniques that is used for selecting and specifically identifying a desired location on the molecule to be engineered (Specification, page 14).

Three-dimensional protein structure determination was well established at the time of the invention and obtaining the 3-D structure of most proteins or enzymes required only routine experimentation. Once the three-dimensional structure of the target molecule is known, a site can be selected by specifically identifying a desired location on the molecule to be engineered. The specification teaches that it may be desirable to select an exposed site on the surface of the target molecule, where the site is available for attachment by the binding molecule (Specification, page 14).

The specification also teaches that an alternative approach to three-dimensional structure analysis is to select target molecular sites that are susceptible to limited proteolysis or sites

strongly predicted to be loops by secondary structure prediction or by analysis of hydrophobic patterns suitable for insertion or replacement engineering (Specification, pages 14). Another alternative approach is to engineer a binding site moiety at random positions within the target molecule. The engineered site is preferably not at the active site of the enzyme but is more preferably located remotely (e.g. at 1-25 Å).

Therefore, one of skill in the art would readily recognize that screening, structural analysis and limited proteolysis analysis are not specific to β-lactamase and can be used with any starting enzyme without undue experimentation.

Moreover, Applicants urge that target and chimeric molecules are prepared by methods readily available to a skilled artisan (Specification, p.12-24). These methods are conventional in the art and are not specific to β-lactamase. Detailed procedures for every embodiment of an invention may not be necessary if the description of the invention itself is sufficient to permit those skilled in the art to make and use the invention [MPEP §2164]. A patent does not teach, **and preferably omits**, what is well known in the art. *In re Buchner*, 18 U.S.P.Q.2d 1331, 1332 (Fed. Cir. 1991); *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 221 U.S.P.Q. 481, 489 (Fed. Cir. 1984). [See also, MPEP § 2164.01].

Applicants, again, direct the Examiner to a recent publication by Ferrer-Miralles et al., *J. Biol. Chem.* 276 (43):40087-40095 (2001), submitted with a previous response. It demonstrates that making galactosidase chimeras according to the teachings of the present invention is fully within the purview of a person of skill in the art. The authors inserted binding site moieties (epitopes of the HIV gp41 glycoprotein in this example) into the sequence of galactosidase. The insertion sites were selected, as described in the present invention, by examining the 3-

dimensional structure of the protein and searching for solvent-accessible loops (compare, e.g., page 14 lines 3-17 of the present application with the first two sentences of the results section – page 40089 – of the Ferrer-Miralles reference). Two insertion sites and several peptide sequences were screened to find enzymes whose activity was modulated through binding interactions with antibodies directed against the epitopes. The molecular biology and enzymology techniques employed by the authors during the screen were standard and can in no way be considered undue experimentation. Hence, this recent publication provides additional confirmation that the technique described in the present application is applicable not only to β-lactamases but also to other types of enzymes.

Therefore, one of skill in the art would be able to practice the presently claimed subject matter in view of the specification and the prior art without undue experimentation. The test for enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 190 U.S.P.Q. 214 (CCPA 1976). See also, MPEP § 2164.01. The fact that experimentation may be complex does not necessarily make it undue if those skilled in the art typically engage in such experimentation. *In re Certain Limited - Charge Cell Culture Microcarriers*, 221 U.S.P.Q. 1165, 1174 (Int'l Trade Comm'n 1983); *M.I.T. v. A.B. Fortia*, 227 U.S.P.Q. 428 (Fed. Cir. 1985); *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988). See also, MPEP § 2164.01.

Thus, Applicants maintain that the experimentation required to practice the instant invention is not undue. The MPEP clearly states:

> As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Failure to disclose other methods by which the claimed invention may be made does not

render a claim invalid under 35 U.S.C. 112. *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 1533, 3 USPQ2d 1737, 1743 (Fed.Cir.), *cert. denied*, 484 U.S. 954 (1987).

[MPEP 2164.01(b), emphasis added]

Accordingly, Applicants submit that the presently claimed subject matter is fully enabling to one of skill in the art. Therefore, the rejection of the claims under 35 USC 112, first paragraph, is improper and should be withdrawn.

2. The Examiner rejects claims 13-29 under 35 USC 112, first paragraph, as allegedly "not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention" (Official Action, page 7).

More specifically, the Examiner argues: "The specification does not describe a representative number of species to the genus" (Official Action, page 8).

Applicants respectfully traverse. The function of the written description requirement is to ensure that a patent is granted to inventors who had possession, as of the filing date of the application relied on, of the specific subject matter later claimed by them; how the specification accomplishes this is not material. *In re Smith*, 178 U.S.P.Q. 620 (CCPA 1973). Therefore, the test for written description under 35 U.S.C. §112, first paragraph, is whether the originally filed specification reasonably conveys to a person having skill in the art that the Applicants had possession of the subject matter later claimed. *In re Kaslow*, 217 U.S.P.Q. 1089 (Fed. Cir. 1983). [See also, MPEP, Section 2163.02].

Applicants respectfully submit that the claims of instant invention are not limited to β-lactamases, which is provided exclusively as an example. "In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass.

One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus" (*Reagents of the University of California v. Eli Lily*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997); See also, MPEP 2163 (III-3(a)), page 2100-161, right-hand column).

The specification clearly defines what Applicants regard as their invention: "In accordance with the present invention, a desired target molecule (TM) can be modified to have at least one binding site moiety (BSM) to which a binding molecule (BM) can attach" (Specification, page 2, lines 10-12). The specification describes the present invention in terms of a generic target molecule (which elsewhere in the specification Applicants note could be an enzyme). The target molecule is modified to have a binding site moiety (which elsewhere in the specification is described as preferably being a mimetope). Nowhere in the specification do Applicants limit the target molecule of their invention to an enzyme and in particular to β-lactamase. On the contrary, the specification provides ten examples of what can be used as a target molecule in a paragraph spanning pages 2 and 3 (Specification, page 2, line 23 – page 3, line 11). One of skill in the art can readily recognize from the original disclosure that Applicants invented the presently claimed subject matter. Therefore, Applicants request that this rejection be reversed.

3. In view of the comments herein, the present application is believed to be in condition for allowance or in better condition for an appeal. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited.

Moreover, Applicants believe that an interview would be helpful in addressing any remaining issues which were not successfully overcome by this Response. Thus, Applicants respectfully request an interview with the Examiner once this Response has been reviewed.

Respectfully submitted,

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